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10/561,571	12/21/2005	Meng Hsin Chen	21406YP	5907

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,571	CHEN ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-15 drawn to compound of Formula I wherein M=CH, M_1= CH, M_2= CH, composition and method of use, in the reply filed on 10/9/2007 is acknowledged. Claims 1-15 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants' traversal of the restriction requirement is not persuasive for reasons of record. As for the traversal, the following apply.

As noted in the previous office action, where there is lack of unity the requirement for restriction is proper- See MPEP 803.02. The requirement for unity of invention is two-fold: (1) common utility and (2) sharing a substantial structural feature disclosed as being essential to the utility. Both these conditions are to be met with. Instant claims do not meet both these conditions.

Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. Applicants have not addressed these two criteria, set forth for restriction requirements.

As for applicants' argument, 37 C.F.R §1.141, states "an applicant may not claim two or more independent and distinct inventions in a single application." As noted above, there are three independent and distinct inventions in the instant case. Hence, the above is not to the point. Secondly, contrary to applicants' assertion, there is no genus-species relationship. The three groups are distinct genus bundled as one in the application. As long as the three inventions lack common utility and substantial structural feature disclosed as being essential to that utility, the restriction as set forth is proper.

Examiner also noted in the previous office action "Should applicant traverse on the ground that the core species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention". Applicants have not asserted that the two groups are not distinct. Applicants have not submitted evidence or identified such evidence now of record showing the core group to be obvious variants or clearly admitted on the record that all core groups embraced in the instant inventions are equivalent. In which case examiner needed not search all cores. A prior art which anticipates any one of the groups embraced by a specific core (i.e. choices of I, II,III) may then render rest of the core groups as obvious variant. In other words, if the examiner finds one of the inventions unpatentable over the prior art,

the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Finally, instant different method of uses claims 8-11, the references provided by the applicants in IDS as well as those now applied clearly shows structurally related compounds of instant claims have different utility, which would negate the common utility requirement & sharing the substantial structural feature.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The continuing data provided by the applicants is not consistent with the PTO records. See BIB DATA SHEET. An appropriate correction is needed.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 12/21/2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Recitation of "X represents $-(CHR_7)_p$ or a bond" in claim 1 renders claim 1 and its dependent claims 2-15 indefinite as it is not clear what is intended. Note when p= 0, X

will be null or a bond. Thus, it is not clear what is the difference between X when p=0 and X a bond.

2. Recitation of " carbocyclic or heterocyclic ring optionally interrupted by 1-3 atoms of O, S, C(O) or NR, ..." in Y definition of instant claim1 renders claim 1 and its dependent claims 2-15 indefinite as it is not clear what is intended. First of the nature of the heterocyclic ring and the heteroatoms and their numbers is not defined clearly. In addition, it is not clear where and how to interrupt the carbocyclic or heterocyclic ring with addition heteroatoms. Note the same in several places of claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating glaucoma or ocular hypertension, does not reasonably provide enablement treating various diseases and preventing repolarization or hyperpolarization of a mammalian cell with intended use to treat various diseases, embraced in the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Method of use claims 9-11 recite treating macular edema, macular degeneration, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension, and/or a neuroprotective, a method of preventing repolarization or hyperpolarization of a mammalian cell, a method of treating Alzheimer's Disease,

depression, cognitive disorders, and/or arrhythmia disorders and method of treating diabetes in a patient in need thereof comprising administering a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof for which there is no adequate written description and enabling disclosure in the specification.

Instant claims 9-11, as recited, are reach through claim. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the blocking of potassium channel in general by the instant compounds, claims 9-11 reach through treating various diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as blockers of potassium channels to effect repolarization or hyperpolarization of a mammalian cell, based on limited assays shown in pages 59-62, it is claimed that treating and or preventing any or all diseases in general for which there is no enabling disclosure. In addition, the scope of these claims include treatment of various specific diseases mentioned above, which is not adequately enabled solely based on the inhibition of potassium channel activity provided in the specification .

From the reading of specification, it appears that the applicants are asserting that the embraced compounds because of their mode action, which involves inhibition of

potassium channel activity to effect repolarization or hyperpolarization of a mammalian cell,, would be useful for besides treating the above said diseases or disorders as well as preventing them. The scope of the claims includes not only treatment but also "prevention of a disease" which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 13 and 59-62.

"To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended mammal. Moreover many if not most of diseases such as macular edema, macular degeneration, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension, Alzheimer's Disease, depression, cognitive disorders, and/or arrhythmia disorders and diabetes are very difficult to treat and hardly possible to prevent as claimed herein. The fact that there are number of such drugs available and that they have not been able to prevent contradicts instant invention. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288 . Also note

Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Cleary et al., Br. J. Opthalmol., 89, 223-228, 2005 and Jenkinson, DH., Br. J. Pharmacol., 147 Suppl. 1, S63-71, 2006.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating or preventing various diseases by inhibiting potassium channel activity.

2) The state of the prior art: Although there are several potassium channel inhibitors are known, they have not prevented or able to prevent and treat various diseases mentioned above embraced in the instant claims. Prior art do not lend support for such a notion. See Ceary et al., and Jenkinson DH., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating and for 'preventive' effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There is no supporting evidence to treat and prevent various diseases embraced by inhibiting potassium channel activity.

6) The breadth of the claims: The instant claims embrace not only treatment but also the prevention of various diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards 'preventing' the variety of diseases of the instant claims, one having ordinary skill in the

art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Boschelli et al., US 5,990,146.

Boschelli et al. teaches several benzimidazole compounds, which include those claimed in the instant claims, for the use as kinase inhibitors useful for treating atherosclerosis and other related diseases. See formula I shown in column 2 and note the definition of Ar, R^1, R^2, R^3 and R^4. Note when instant W= R_9, the compounds taught by Boschelli et al. include instant compounds. See column 2-14 for various preferred embodiments. Particularly, see column 14-38, examples of 1-66 for compounds made.

Claims 1, 2, 4, 5, 6 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Willoughby et al., US 6,531,484.

Willoughby et al. teaches several benzimidazole compounds, which include those claimed in the instant claims. See column 53-56, Scheme 18 & 19. See amine-1 to amine-6 shown in column 64-66 for compounds made.

Claims 1, 2, 4, 5, 6 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Chapman et al., US 6,248,755.

Chapman et al. teaches several benzimidazole compounds, which include those claimed in the instant claims. See column 127 Scheme 15. See Table 8 shown in column 199-200 for compounds made.

Claims 1-6, 8 and 12-15 rejected under 35 U.S.C. 102 (b) as being anticipated by Yamasaki et al., US 6,352,985.

Yamasaki et al. teaches several benzimidazole compounds for treating glaucoma, which include those claimed in the instant claims. See column 2, formula I and note the definition of R_1, R_2, R_3, and R_4 groups. Note with the given definition of these variable groups compounds taught by Yamasaki et al., include instant compounds. See column 2-19 for preferred embodiments and process of making these compounds. See column 29-39 and figure 1-58 for various species made. See also column 41-162 for examples 1-322.

Claims 1, 2, 4, 6 and 12 rejected under 35 U.S.C. 102 (b) as being anticipated by Houlihan US 4,212,876.

Houlihan teaches several benzimidazole compounds for treating obesity which include those claimed in the instant claims. See formula shown in column 1, and note the definition of R_1 and R_2 groups. Note with the given definition of these variable groups, compounds taught by Houlihan include instant compounds. See column 1-4 compounds.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624

12/17/2007